



TITLE:

Pulmonary hemorrhage induced by epileptic seizure.

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Keywords: hemoptysis; epileptic seizure; capillary permeability; alveolocapillary membrane.

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Abstract: Abstract

We report a 35-year-old man who presented with pulmonary hemorrhage induced by an epileptic seizure. He had experienced recurrent episodes of massive hemoptysis after epileptic seizures since the age of 28. He was admitted to our hospital with massive hemoptysis and hypoxia after an epileptic seizure of a few minutes' duration. Radiographic signs of infiltrations and hemorrhagic bronchoalveolar lavage fluid were observed. He was intubated, and successfully treated with anti-epilepsy drugs and corticosteroids. Epileptic seizures may have induced increased pulmonary vascular permeability and structural damage to the blood-gas barrier, which may have caused pulmonary hemorrhage. Pulmonary hemorrhage could be in the list of differential diagnoses of hemoptysis in patients with epilepsy.

Dr. Nancy Redeker
Editor of *Heart & Lung*

Dear Dr. Nancy Redeker,

Enclosed please find the revised version of our manuscript entitled “Pulmonary hemorrhage induced by epileptic seizure.” We are very grateful to you and the reviewers for the helpful comments on the original version of our manuscript. We have made every effort to prepare the revised version accordingly. As you suggested, we emphasized clinical implications of our case in the abstract and in the conclusion. The revised parts of the manuscript have been written in red.

We hope that you will find this revised version of our paper suitable for publication in *Heart & Lung* and look forward to hearing from you at your earliest convenience.

Sincerely yours,

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Our point-by-point responses to the Reviewer's comments are as follows.

Responses to Reviewer #1

Comment I.

I would recommend modifying the abstract - should talk more about pulmonary hemorrhage rather than hospital course.

Response.

Thank you very much for your valuable comment. Explanation of clinical implication was insufficient, and we have added a short paragraph in the abstract to better explain the significance of this paper. At the same time, we shortened the description of the hospital course.

Comment II.

On page 4 description of noncompliance is lengthy may which can be shortened.

Response.

We agree with the Reviewer's comment, and we have summarized the description (Page 5, line 6-8).

Comment III.

On page 8 reference to animal experiment is cited - not sure if needed.

Response.

We agree that animal experiment doesn't fit discussion of this human case, and we have deleted the reference.

Comment IV.

Too many references for case report unless it is alright with the journal.

Response.

As suggested by the Reviewer's comment, references were too many. We have selected 9 from the initial 14 references.

Pulmonary hemorrhage induced by epileptic seizure

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Abstract

We report a 35-year-old man who presented with pulmonary hemorrhage induced by an epileptic seizure. He had experienced recurrent episodes of massive hemoptysis after epileptic seizures since the age of 28. He was admitted to our hospital with massive hemoptysis and hypoxia after an epileptic seizure of a few minutes' duration. Radiographic signs of infiltrations and hemorrhagic bronchoalveolar lavage fluid were observed. He was intubated, and successfully treated with anti-epilepsy drugs and corticosteroids. Epileptic seizures may have induced increased pulmonary vascular permeability and structural damage to the blood-gas barrier, which may have caused pulmonary hemorrhage. Pulmonary hemorrhage could be in the list of differential diagnoses of hemoptysis in patients with epilepsy.

Key words

hemoptysis; epileptic seizure; capillary permeability; alveolocapillary
membrane.

Abbreviation list

GTCS, generalized tonic-clonic seizures; FDP, fibrin degradation product;
HRCT, high resolution computed tomography; NPE, neurogenic pulmonary
edema; BGB, blood-gas barrier.

Introduction

The development of pulmonary hemorrhage is associated with a variety of diseases such as collagen diseases, systemic vasculitis and mitral stenosis. Epileptic seizure is uncommon as a cause of pulmonary hemorrhage, with only one case being reported [1]. Here, we report a case of pulmonary hemorrhage induced by epileptic seizures.

Case report

The patient was a 35-year-old man who had had tuberculous meningitis at the age of 2, and thereafter experienced epileptic seizures intermittently. He was diagnosed as having left mesial temporal lobe epilepsy. Primarily, his seizures consisted of complex partial seizures and, secondarily, generalized tonic-clonic seizures (GTCS). He frequently did not take his antiepileptic drugs and frequently missed outpatient appointments based on his own judgment, resulting in recurrent seizures. Since the age of 28 years, he had repeated GTCS followed by massive hemoptysis that filled a drinking glass while not taking his medications. Hemoptysis never followed a complex partial seizure when GTCS did not also occur. He was a never-smoker and his occupation was system engineering. He had no history of any other medical illness.

He presented at the emergency room of our hospital with massive hemoptysis after an epileptic seizure of a few minutes' duration. He had discontinued taking antiepileptic drugs (valproic acid and carbamazepine) for a week previously. The plasma levels of valproic acid and carbamazepine were 19.0 μ g/ml (therapeutic plasma level: 40-120 μ g/ml) and 2.0 μ g/ml

(therapeutic plasma level: 3-10 μ g/ml), respectively. On admission, he was awake and alert, with a body temperature of 37.8°C, blood pressure of 140/41 mmHg, pulse rate of 107 beats per minutes and respiratory rate of 40 breaths per minutes. He needed an oxygen reservoir mask with 7L/min flow to maintain his oxygen saturation in the normal range (Table 1). Except for a high white blood cell count and an increased fibrin degradation product (FDP) level, the results of all other laboratory tests, including autoantibody tests and coagulation system studies, were within normal range (Table 1). Chest radiography on admission showed diffuse infiltrative opacities throughout both lungs (Fig. 1A). Chest high resolution computed tomography (HRCT) revealed diffuse ground-glass and infiltrative opacities in bilateral lungs (Fig. 1B). He was admitted to the intensive care unit and intubated. With fiberoptic bronchoscopy, an effusion of blood poured from every branch of the peripheral areas in both lungs. Examination of bronchoalveolar lavage fluid from the left B⁴ bronchus showed an elevated total cell count with dominance of neutrophils (85%) with a few hemosiderin-laden macrophages. With the diagnosis of diffuse pulmonary hemorrhage, we administered methylprednisolone 1 g/day for 3 days

intravenously. On the next day, the output of blood from the intratracheal tube was decreased and the P/F ratio improved from 146 mmHg to 404 mmHg. On the third day of the admission, he was extubated and noninvasive positive pressure ventilation was introduced up to the 10th day. On the 8th day, all traces of blood in the sputum had disappeared. Infiltrates in both lungs were no longer evident on chest X-ray and HRCT taken on the 12th day (Fig 2). 60 mg/day of oral prednisolone was administered from day 4 and tapered to 20 mg/day while under care in **the** outpatient clinic. He was discharged on the 19th day.

Discussion

Systemic vasculitis and collagenous diseases (Goodpasture's syndrome, ANCA-associated vasculitis, systemic lupus erythematosus, etc.), heart diseases (mitral stenosis, etc.) and exogenous factors (chemicals, drugs, etc.) are known as causes of pulmonary hemorrhage. In our case, systemic vasculitis, collagenous diseases, malignant disease, tuberculosis and fungal infections were ruled out. Echocardiography did not reveal evidence of valvular disease or heart failure. Pulmonary hemorrhages induced by overdoses of carbamazepine or valproic acid have been reported [2][3]; however, this was unlikely in our case because the blood concentration of these drugs on arrival was much lower than the effective doses.

In the present case, neurogenic pulmonary edema (NPE) accompanying epileptic seizures could have been the cause of the hemoptysis. NPE occurs with central nervous system disorders, such as brain trauma, subarachnoid hemorrhage, bleeding in the brain parenchyma, spinal cord injury, and epileptic seizure. The hypothalamus and medulla oblongata seem to induce increases in pulmonary hydrostatic pressure and pulmonary vascular permeability via the autonomic nervous system [4]. The clinical symptoms of

NPE are hypoxia with diffuse pulmonary infiltrates, which improves within a few days. Our patient had a similar clinical course, leading to the speculation that the same mechanisms might be present. However, since massive hemoptysis is atypical as a symptom of NPE, the present patient's condition cannot be explained by NPE.

As another possible mechanism, pulmonary hemorrhage and various degrees of hemoptysis induced by severe exercise have been reported [5-7], in which structural dysfunction of the blood-gas barrier (BGB) is considered as the cause. The BGB in the human lung is very thin to allow for adequate gas exchange by passive diffusion; the thickness is only 0.2-0.3 μ m over more than half of the total surface area of the lung. During heavy exercise in normal subjects, the capillary pressure near the base of the lung has been estimated to exceed 35 mmHg, a level that exerts great stress on the capillary endothelium [8]. These changes destroy the function of the alveolar septal barrier and allow the development of pulmonary hemorrhage and various amounts of hemoptysis. Ueno et al. reported a patient with frequent epileptic seizures in whom transient pulmonary hypertension reached 70 mmHg [9]. Thus, epileptic seizures can be considered to induce increased

capillary pressure followed by structural damage of the BGB. This mechanism is supported by the fact that in our patient hemoptysis never followed a complex partial seizure without the occurrence of GTCS. In our case, these hemodynamic and structural changes are considered to be the cause of pulmonary hemorrhage.

In conclusion, we described a case of pulmonary hemorrhage induced by epileptic seizure. Epileptic seizures could induce increased pulmonary vascular permeability and structural damage to the BGB. In an epileptic patient with hemoptysis, pulmonary hemorrhage should be considered. In such a critical case, tighter control of epilepsy is required to avoid recurrence of the hemorrhage.

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Figure legends

Figure 1. Chest roentgenogram (A) and HRCT scan (B) on the admission day. Diffuse ground-glass and infiltrative opacities in bilateral lungs were revealed.

Figure 2. Chest roentgenogram (A) and HRCT scan (B) on the 12th day after admission. The ground-glass opacities had completely resolved.

Abstract

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Figure





Figure





Table 1. Laboratory findings upon admission

Hematology			Serology		
WBC	17,000	/ μ l	CRP	0.1	mg/dl
Hb	14.5	g/dl	RF	0.2	IU/ml
Plt	18.9 \times 10 ⁴	/ μ l	ANA	< \times 40	
Chemistry			Anti Jo-1 ab	<5	U/ml
TP	6.7	g/dl	Anti Sm ab	<5	U/ml
AST	26	IU/l	Anti SS-A ab	<5	U/ml
ALT	40	IU/l	Anti SS-B ab	<5	U/ml
LDH	247	IU/l	Anti Scl-70 ab	<5	U/ml
BUN	10	mg/dl	MPO-ANCA	<10	EU
Cr	0.8	mg/dl	Anti GBM ab	<10	EU
Coagulation			Urinalysis		
PT (sec)	11.6	sec	protein	(\pm)	
PT (INR)	1.07		occult blood	(—)	
aPTT	26.6	sec			
Fib	177	mg/dl			
D-dimer	1.5	μ g/ml			